2.07

12.

A CASE OF "ACUTE LEUKÆMIA" WITH A SCHEME OF CLASSIFICATION OF LEUKÆMIAS AND PSEUDO-LEUKÆMIAS.

BY

F. PARKES WEBER.

Reprinted from the 'Transactions of the Pathological Society of London,' Vol. 54, Part III, 1903.

ROYAL COLLEGE OF SURGEONS OF ENGLAND
LIBRARY

LONDON:
PRINTED BY ADLARD AND SON,
BARTHOLOMEW CLOSE, E.C.

1903.

ROYAL COLLEGE OF SURGEONS OF ENGLAND
13 JAN

Reprinted from the 'Transactions of the Pathological Society of London,' 1903.

A case of "acute leukæmia," with a scheme of classification of leukæmias and pseudo-leukæmias.

By F. Parkes Weber.

A very anæmic man, Wilhelm R—, a native of Germany, aged 49 years, was admitted into the German Hospital for purpura, etc., on September 13th, 1902, and died on the following day. I did not see the man myself during life, but notes were taken by the house physician, Dr. Quosig. According to the patient's wife his illness commenced about eight weeks before his death. The gums were swollen and bled easily, and he had spots on the skin. He suffered from pain in the throat, headache, and pains in the back, and lost flesh. Previously to the final illness he seems generally to have enjoyed good health. There was no history of syphilis or alcoholism. His wife, who looked healthy, had had eight children (four were still living, four dead) and four miscarriages. About twelve months ago he had some abdominal discomfort and pain. He once had influenza, and had often suffered from his throat, but paid little attention to it.

Condition on day of admission (September 13th, 1902).—The patient was very anæmic, and there were dark violet-red cutaneous petechiæ over the whole body. Temp. 100° F. Pulse about 114 in the minute. Dyspnœa. There was a kind of muttering delirium, but he could answer questions. The breath had an offensive smell. The gums were pale and swollen, the tonsils were enlarged so as almost to touch each other, and the uvula was œdematous. The tongue was moist and somewhat coated. On the left cheek there was a dark reddish circumscribed swelling about the size of a small chestnut, which was discharging a thin purulent material from an opening in its centre. According to the patient this lump had been present eight days. The cervical, axillary, and inguinal lymphatic glands were moderately enlarged. Slight bronchitic sounds were heard over the lungs, and a systolic murmur was audible over the apex of the heart. The spleen was enlarged, and the lower edge could be felt three finger-breadths below the ribs.

The liver was perhaps enlarged. No ascites. Œdema about the ankles. Knee-jerks active. Slight ankle-clonus. Plantar reflexes natural. Sensation natural. Pupils equal, react to light. Urine: sp. gr. 1012, acid, some albumen, no sugar.

Next morning the patient's temperature was 100·4° F. In spite of strychnine and subcutaneous transfusion of normal salt solution the weakness steadily increased, and death occurred about 5 p.m.

The Blood.

The blood was unfortunately not examined during life. That present in the heart at the *post-mortem* examination had a peculiar brownish-pink appearance, as if it were mixed with milk, and films were taken for microscopical examination. There was no poikilocytosis, and the erythrocytes were well preserved, as was well seen on examining blood in sections of the tissues. The white cells were immensely increased in number, in some parts occupying nearly as much of the field as the red cells, yet after examination of the blood in blood-vessels seen in the microscopic sections of the organs I think that the relative proportion of white cells to red cells would have been found to be much less had the blood been examined during the patient's life. Dr. G. L. Eastes kindly made the following differential count of the white cells for me:—Small lymphocytes 36·4 per cent., large lymphocytes 56·3 per cent. (total lymphocytes 92·7 per cent.), polymorphonuclears 0·2 per cent., eosinophiles 1·1 per cent., myelocytes 2·4 per cent., eosinophile myelocytes 3·6 per cent. This count represents the composite result arrived at by counting a fairly large blood film in five different parts, 200 white cells being enumerated in each part. The size of the lymphocytes appeared to depend upon the thickness with which the blood was spread. Dr. Eastes thought that the lymphocytes were in general of medium size, tending rather to the large than the small form. The percentages of the other cells present varied in different parts of the same film. He found about one erythroblast per 100 white cells.

Necropsy.

The heart weighed fourteen ounces. There was no pericardial effusion, but there was a localised patch of pericarditis over the middle of the front of the heart,[1] and many petechiæ under the visceral layer of the pericardium. The cardiac muscle was exceedingly pale and flabby. There was no valvular disease.

The *lungs* were somewhat œdematous. There was a little scarring at both apices, and old pleuritic adhesion over part of the right lung.

The *spleen* was enlarged, weighing twenty-six ounces, and was of a soft "chocolate pudding" consistence and colour.

The *liver* was enlarged and very pale. It weighed ninety-six ounces. Microscopic examination accounted for some of the increase in weight of the organ, for the interlobular spaces were found packed with leucocyte-like cells, the distribution of the change resembling that of the interlobular cell-infiltration in commencing hepatic cirrhosis. I shall later on return to the microscopic examination.

The *kidneys* were pale, and weighed sixteen ounces together. The capsules stripped readily. A minute whitish patch in the cortex of one kidney was examined microscopically, and showed an accumulation of leucocyte-like cells similar to those in the interlobular spaces of the liver. I shall later on describe the microscopic characters of these cells.

The *pancreas* macroscopically showed nothing noteworthy.

The *stomach* showed petechial submucous hæmorrhages. In the intestines nothing abnormal was seen, but they were very incompletely examined.

All the mesenteric *lymphatic glands* were considerably enlarged. One of them from near the hilum of the liver was selected for microscopic examination (see later).

The *brain* (weight fifty-one ounces) showed nothing abnormal except that the pia mater seemed to be infiltrated with blood.

Of the enlarged superficial lymphatic glands of the body the supra-condylar gland from one elbow was removed for microscopic examination (see later).

Bones.—One femur and one humerus were examined. The cancellous tissue in the head of each of these bones contained pale marrow, but the marrow in the shafts was chiefly of a creamy brownish-red colour, sometimes seen in the contents of a liver abscess, but not diffluent. A piece of this marrow from the shaft of the humerus was removed for microscopical examination (see later). The sternum and ribs contained reddish marrow. A shoulder-joint and a hip-joint were examined and appeared normal.

---

[1] This patch apparently corresponded to the "milk-spot" often seen on the front of the heart, and confirms the view that such "milk-spots" may sometimes be due to a former patch of pericarditis ("epicarditis").

Microscopic examination.

Sections were made (1) of the bone marrow from the shaft of the humerus; (2) of a piece of the spleen; (3) of two lymphatic glands; (4) of a piece of the liver; and (5) of a piece of a kidney. The methods of staining employed were—(*a*) hæmatoxylin or hæmatoxylin and eosin; (*b*) Ehrlich's triacid mixture; (*c*) Mann's long method by the biacid mixture of methyl blue and eosin.[1]

(1) *The bone marrow from the shaft of the humerus.*—The space normally occupied by fat-vesicles is much encroached on by blood and leucocyte-like cells. The whole tissue may be said to be permeated [2] with these colourless cells, almost all of which can be divided into two kinds:

(A) Mononuclear cells without distinct granules, of about the diameter of a red blood-corpuscle on the average and evidently of the same nature as the lymphocyte-like cells in the man's blood, though many of them have rather more protoplasm around the nucleus. Almost all these cells are mononuclear, but the nucleus is often not spherical; sometimes it is indented on one side, sometimes it is lobed, and sometimes there are two or three nuclei in the same cell.

(B) Granular mononuclear cells, apparently of the myelocyte class. By Mann's eosin-methyl-blue method the granules of these cells are more or less coloured by the eosin, and many of the cells can be termed coarsely granular eosinophile. They are, on the average, slightly bigger than the preceding class of cells (A), and have relatively more protoplasm. The nucleus, which has frequently an eccentric position on one side of the cell, is not always round. It is sometimes elongated, and sometimes appears to be undergoing division, and sometimes there are two nuclei in the same cell.

---

[1] *Vide* G. Mann, 'Physiological Histology,' 1902, p. 216.

[2] I have avoided saying that the tissues are "*infiltrated*" with the cells, because the word "infiltrated" implies that the cells have been deposited in the tissues from the blood, a conclusion which I think is not yet justified in regard to cases like the present one. For the same reason I have in this paper altogether avoided speaking of leukæmic or lymphocytic "*infiltration*" or "*deposit*." The word "*permeated*" was kindly suggested to me by Dr. A. E. Garrod as a way out of the difficulty.

In most parts the non-granular cells (Class A) are more numerous than the granular cells (Class B), but in some parts the two classes of cells appear equally numerous.

(2) *The spleen.*—The splenic tissue is permeated with cells of the two classes described as A and B in the preceding description of the bone marrow; it is doubtless in great part to this that the organ owes its increase in size and weight. I will not describe these cells again. In many parts the granular cells (B) are as numerous as the non-granular lymphocyte-like cells (A), and in some parts even more numerous; but in most parts the non-granular cells (A) are more numerous, and the cells in the Malpighian corpuscles belong almost entirely to the non-granular class.

(3) *The lymphatic glands.*—Amongst the non-granular lymphocyte-like cells there is throughout a good admixture of granular cells similar to those described as Class B in the account of the bone-marrow; in some parts of the sections the granular cells are very numerous.

(4) *The liver.*—I have already described the change in this organ, and have only to add that the leucocyte-like cells, which have chiefly accumulated between the lobules (interlobular distribution), but likewise to a lesser extent between the columns of hepatic cells (intercellular distribution), are partly of the non-granular lymphocyte-like class (A), and partly of the granular class (B). The former (A) are decidedly the most numerous, though in some parts of the sections there is a good proportion of the latter (B).

(5) *The kidney.*—In some parts of the patch permeated with leucocyte-like cells[1] already referred to, the lymphocyte-like cells (Class A) predominate, but in other parts the granular cells (Class B) seem to be as numerous or even more numerous.

I must thank Mr. S. G. Shattock and Dr. J. H. Drysdale for kindly looking over the microscopic specimens with me, and

---

[1] I do not use the term leukæmic "infiltration" or leukæmic "deposit" for the reason given in a former foot-note.

Professor R. Muir, of Glasgow, for kindly examining sections of the bone-marrow, spleen, and liver. I was particularly anxious to have Professor Muir's opinion about the granular cells in the affected tissues. He writes, "I have examined the sections you sent me, and I have no doubt that the cells in question are eosinophiles. Some of them, especially in the spleen and marrow—in fact, a large proportion of them in these two sites,—have the characters of eosinophile myelocytes. I have never seen eosinophile cells in such numbers in the tissues in lymphatic leukæmia, yet the case appears to be of that nature."

Remarks.

A good many cases of "acute leukæmia" have been published, and I must refer to the papers by W. Ebstein,[1] by A. Fraenkel,[2] by J. Rose Bradford and H. Batty Shaw,[3] by A. G. Phear,[4] etc., for an account of the subject. I shall only consider some of the numerous questions which arise.

The stomatitis, tonsillitis, and signs of microbic infection in acute leukæmia cases of this class have been supposed to separate them pathologically as well as clinically from the more chronic cases. This deduction is, however, scarcely justified as yet. An unhealthy condition of the gums and mouth may occur in many conditions other than acute leukæmia,—for instance, in chronic leukæmia, in splenic anæmia (including Banti's disease), in Hanot's disease, etc. It is quite possible, therefore, that the stomatitis and microbic infection may not be the cause of the blood-change with which they are associated in cases of acute leukæmia. There is no satisfactory clinical evidence that acute leukæmia is infectious, for Obrastzow's[5] apparent instance of infection is not sufficient.

---

[1] "Ueber die acute Leukämie und Pseudoleukämie," 'Deut. Arch. für klin. Medicin,' 1889, vol. xliv. p. 343.

[2] "Ueber acute Leukämie," 'Deut. med. Wochenschrift,' 1895, Nos. 39—45.

[3] "Five Cases of Acute Leukæmia," 'Medico-Chirurgical Trans.,' London, 1898, vol. lxxxi, p. 343.

[4] "A Case of Acute Leukæmia," 'Medico-Chirurgical Trans.,' London, 1901, vol. lxxxiv, p. 453.

[5] "Zwei Fälle von acuter Leukämie," 'Deut. med. Wochenschrift,' 1890, No. 50, p. 1150. A young man aged 17 years, in the Alexandra Hospital at Kiev, died of acute leukæmia about four weeks after the first symptoms of the disease. He had gangrenous ulceration of the soft palate, and abundant

In the present case the clinical history is typical, but, as in most cases, there is no absolute evidence to show when the changes in the blood first commenced.

In all or nearly all cases of acute leukæmia the blood-changes seem to have been those of lymphatic leukæmia, the increase in the colourless corpuscles of the blood being mainly due to the great number of cells of the large and small lymphocyte types. Obrastzow's two cases,[1] like a few others, were possibly exceptions, for he says that the white blood-cells in both cases were chiefly mononuclear and "faintly granular."

The present case is remarkable amongst cases of acute leukæmia on account of the great number of myelocyte-like cells present in the blood-forming tissues, yet the greater proportion of colourless cells both in the blood and in the tissues belonged to the lymphocyte type. The term *acute lymphatic leukæmia* is therefore justified for this case, as for most other cases of "acute leukæmia." Yet it is probable that cases of "acute leukæmia," such as the present one and Obrastzow's two cases,[2] ought to be regarded as representing a primitive and *relatively undifferentiated form of leukæmia* (see later on), characterised by extremely rapid progress and by all the leucocyte-forming tissues being involved at once. It is, however, also possible that, as in many cases of "acute leukæmia" there has been evidence of microbic infection as well as of leukæmia, the presence of granular cells in the blood and tissues may represent a reaction to such infection, complicating the signs of lymphatic leukæmia. On the whole, "acute leukæmia" is probably a more primitive or less differentiated type of disease than the more chronic forms of lymphatic leukæmia; but doubtless "intermediate cases" occur, and there is no hard and fast line to be drawn. Typical "spleno-medullary leukæmia" is probably the most "highly differentiated" form of leukæmia.

The question arises, whence are the lymphocyte-like cells in

micrococci were found *post mortem* in one of the lymphatic glands. Forty-one days after this patient's death a rather thin and pale man aged 32, who had attended on him in the hospital, fell ill himself with acute leukæmia, and developed a kind of hæmorrhagic stomatitis. He died fourteen days after the commencement of the symptoms.

[1] Loc. cit. See also remarks in the addendum at the end of my paper.

Loc. cit.

the blood of cases of lymphatic leukæmia derived? Excluding possible multiplication in the blood-stream itself, are they found solely in the lymphatic glandular tissues of the body (spleen and lymphatic follicles and glands), as some have maintained,[1] or are they formed also in the bone-marrow? Their abundance in the bone-marrow in many cases has suggested the view that the bone-marrow is one of the sites of their production, and that it is not merely infiltrated from the blood-stream by cells produced in the lymphatic glands and spleen. But the recent observations of A. Dennig[2] and C. H. Melland[3] seem to settle this question conclusively. They have each of them published a case of acute lymphatic leukæmia (lympho-cythæmia) in which *post mortem* practically no change was discovered in the leucocyte-forming tissues other than the bone-marrow, thus proving that not only may the lymphocyte-like cells in the blood be partly derived from the bone-marrow, but even that in some cases of the disease the bone-marrow may be the almost exclusive site of their production.

This point leads me to the subject of the origin of the other forms of white corpuscles seen in leukæmic blood, and the nature of the different forms of leukæmia.

Granting that in healthy persons the lymphocytes are exclusively formed in the lymphatic glandular tissues of the body, and that the neutrophile myelocytes are the parents of the polymorphonuclear leucocytes of the blood, and are only found in the bone-marrow, it does not follow that the same rule is maintained in cases of leukæmia. If we admit that a non-granular cell of the large lymphocyte type, normally seen in the germinating centres of lymphatic glands, is the predecessor in the lymphatic glandular tissues of the ordinary lymphocytes, and in the bone-marrow of the granular myelocytes (and thus indirectly of the polymorphonuclear leucocytes of the blood),[4] the following "tumour-formation" theory of the various kinds of leukæmia appears the most probable, or at least the most plausible.

---

[1] Prof. R. Muir (Allbutt's 'System of Medicine,' vol. v, p. 642), speaking of the bone-marrow in lymphatic leukæmia, says, "The condition is really a lymphocytic infiltration of the bone-marrow, this tissue being secondarily affected in the same way as other organs."

[2] 'Muenchener med. Woch.,' January 22nd, 1901, No. 4, p. 140.

[3] 'Medical Chronicle,' September, 1902, p. 372.

[4] *Vide* the various writings of A. Pappenheim and other authors on the subject.

(1) All forms of leukæmia are to be regarded as due to a *hyperplasia-like tumour-formation* in the leucocyte-producing tissues of the body, the tumour-cells (which more or less resemble true leucocytes) overflowing or being attracted out into the blood-stream. (2) If in this tumour-formation the less differentiated (more primitive) cells, viz. the non-granular cells of the large lymphocyte type, either those of the lymphatic glandular tissues or those of the bone-marrow, or those of both, be the cells chiefly involved (that is, if they are to be regarded as the "parents of the tumour-cells"), the result will be a condition of lymphatic leukæmia (lympho-cythæmia), and in the most acute cases the blood will generally contain more cells of the large lymphocyte type than cells of the small lymphocyte type. (3) If, on the other hand, the more differentiated cells, viz. the granular cells of the bone-marrow, be the cells chiefly involved in the tumour-formation, the result will be a condition of myelogenic or spleno-medullary leukæmia, and the tumour-cells in the tissues and blood will resemble myelocytes and ordinary polymorphonuclear leucocytes. (4) "Spleno-medullary" leukæmia, according to this theory, is to be regarded as a higher and more differentiated type of disease than lymphatic leukæmia (that is, it is to be regarded as due to a tumour-formation of a less embryonic type), and this supposition agrees with the fact that in its development and course it is generally less rapid. (5) In some cases of leukæmia, especially spleno-medullary leukæmia, it is possible that cells of the large lymphocyte type in the lymphatic glands and spleen may become granular like similar cells in the bone-marrow normally do. That is to say, it is possible that the myelocyte-like cells found in the spleen and lymphatic glands in such cases have not merely been deposited there from the blood-stream, but may have developed *in situ* from cells of the primitive large lymphocyte type. (6) According to this theory any leukæmia differs from any leucocytosis (including lymphocytosis) in that the former is due to an inroad of tumour-cells from a hyperplasia-like tumour-formation in the leucocyte-producing tissues of the body, whilst the latter is merely the expression of a tissue reaction which may occur in health as well as in disease. A leucocytosis is therefore, strictly speak-

ing, never an early stage of leukæmia; yet a true leucocytosis may perhaps be followed by true leukæmia, in so far as a reactive growth in the leucocyte-producing tissues (of which reactive growth the leucocytosis is the expression) may be supposed to give a start to a tumour-formation (of which the leukæmia is the expression), just as chronic irritation of the skin sometimes acts as the exciting cause of epithelioma.

If we carry this theory a little further all primary hyperplasia-like tumour-formations in the leucocyte-producing tissues of the body may be regarded either as leukæmias or as pseudo-leukæmias (using the German terms for convenience), and the question arises, why do the newly formed cells escape (overflow or become attracted) into the blood-stream in cases of leukæmia, and not in cases of pseudo-leukæmia? In the pseudo-leukæmias the tumour cells, though more or less closely resembling leucocytes, and originally derived from the leucocyte-forming tissues of the body, may have become so modified in the process of tumour-formation that, unlike the leucocyte-like cells of leukæmia, they may have lost the power of entering (being squeezed into or attracted into) the blood-stream, or have lost the power of persisting in a living state in the circulating blood. I do not think, however, that the main difference between a leukæmia and a pseudo-leukæmia can be explained merely on the mechanical theory that when the bone-marrow is the site of a rapid growth the contents of the medullary cavity are likely to be partly forced out into the blood-stream, owing to the fact that they are confined by walls which, unlike the capsules of the spleen and lymphatic glands, are rigid and scarcely distensible.[1] In some cases of multiple myeloma all the ribs have been crammed full and even bulged out with growth, and yet there has been no escape of cells into the circulating blood sufficient in amount to notably increase the proportion of colourless corpuscles.

It seems to me that the whole class of leukæmias and pseudo-leukæmias may be divided into the following six types, independently of intermediate forms:

(A) A new growth of lymphocyte-like cells originating in the bone-marrow and not overflowing into the circulating blood. Myelogenic pseudo-leukæmia (using leukæmia in the sense of lympho-cythæmia), myelogenic lympho-sarcoma, lymphadenomatosis of bones, multiple myeloma (myelomatosis) of the lymphatic type.

---

[1] See A. Pappenheim, 'Virchow's Archiv,' 1901, vol. clxvi, p. 473.

(B) Similar to the preceding, but the lymphocyte-like cells enter or are drawn into the blood-stream. Myelogenic lymphocythæmia (viz. some cases of acute lymphatic leukæmia).

(C) A new growth formed in large part of lymphocyte-like cells originating in the lymph-glands, or lymphadenoid tissues generally, and not to any great extent overflowing into the circulating blood. Lymphatic or splenic lymphadenoma or pseudo-leukæmia (using leukæmia in the sense of lymphocythæmia), Hodgkin's disease. In the more chronic and fibrous varieties of this type the microscopic appearances differ of course considerably from those in acute cases.

(D) Similar to the preceding, but the lymphocyte-like cells invade the blood-stream. Lymphatic or splenic lympho-cythæmia.

(E) A new growth of cells derived from the myelocytes of the bone-marrow and not invading the circulating blood. Myelogenic pseudo-leukæmia (using leukæmia in the sense of myelogenic or spleno-medullary leucocythæmia). To cases of this type or partaking of this type the term multiple myeloma (myelomatosis) might perhaps be limited.

(F) A new growth characterised by its myelocyte-like cells overflowing into the circulating blood. Bence-Jones albumosuria never occurs in this type, though it sometimes does in the preceding type (E). *May* 19*th*, 1903.

Addendum.

SINCE writing this paper an article on "Acute Myelogenic Leukæmia," by Dr. Billings and Dr. Capps, has appeared in the 'American Journal of Medical Sciences' for September, 1903 (p. 375). They regard the faintly granular, large mononuclear cells in the blood of Obrastzow's and similar cases as myelocytes or transitional cells. Their views are not much at variance with those here expressed.

The bone-marrow must be the source of the great increase of the so-called "lymphocytes" in the blood of those cases of acute leukæmia in which the bone-marrow is practically the only one of the leucocyte-forming tissues involved—no matter whether these cells be termed "lymphocytes," or "non-granular myelocytes," or "myelocytoblasts" which have not yet had time to form granules in their cell-protoplasm. I incline to the view that cells of the large non-granular mononuclear type, whether in the bone-marrow, or in the lymphatic glandular tissue, or in both of them, can give rise not only to cells of the ordinary lymphocyte type, but also to cells of the myelocyte type. All varieties of leukæmia can be accounted for in this way. In Dr. Wilkinson's case ('Lancet,' 1903, vol. i, p. 1739) the blood condition is said to have changed from one of myelogenic leukæmia to one of lymphatic leukæmia. The lymphatic glands were not felt enlarged. No *post-mortem* examination was obtained, but I think that the change in the type of the blood-cells may very well be explained by supposing the bone-marrow disease to have become more acute. Thus the leukæmic condition of the blood would become "less differentiated," *i. e.* the large non-granular mononuclear cells (lymphocyte-like cells) would remain undifferentiated, not having time to develop into granular cells of the myelocyte type. Doubtless also in acute exacerbations of chronic myelogenic leukæmia, as well as in primarily acute myelogenic leukæmia, the blood may show an enormous increase of cells of the large mononuclear (lymphocyte-like) type.

An important physiological deduction from a study of cases of "multiple myeloma of the lymphatic type" (*i. e.* lymphadenomatosis ossium) and cases of acute lymphocythæmia, in which the bone-marrow is the only one of the blood-forming tissues involved, is that all the granular myelocytes (and consequently all the polymorphonuclear leucocytes of the blood-serum) are to be regarded as normally derived from cells of the lymphocyte type, *i. e.* as being *differentiated lymphocytes.* When an extremely rapid formation of myelocytes is attempted (hyperplasia-like tumour-formation in the bone-marrow) there is no time for the development of granules in the cell-protoplasm, and consequently cells resembling large and small lymphocytes, not myelocytes, are produced.

In my classes A and B of the group of leukæmias and pseudoleukæmias, instead of supposing that the lymphocyte-like cells are derived from the non-granular predecessors of the myelocytes, I would now suggest that they are derived from the myelocytes themselves by the latter losing their granulation in the process of proliferation, and consequently reverting to the lymphocyte-like (embryonal) type of their ancestors. According to this theory the large lymphocyte-like cells would represent ordinary large myelocytes, and the small lymphocyte-like cells (generally fewer in number) would represent particularly small myelocytes.

PRINTED BY ADLARD AND SON, LONDON AND DORKING.